Developing Inhibitors of VEGF-C/VEGF-D

Circadian Technologies
(ASX:CIR, OTCQX:CKDXY)

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Corporate Summary

- Extensive worldwide intellectual property platform in respect of VEGF-C, VEGF-D and VEGFR-3
- Lead compound OPT-302 blocks VEGF-C and VEGF-D
- OPT-302 in development for treatment of wet AMD
- Potential in a range of eye diseases as a monotherapy or in combination with approved anti-VEGF-A therapies
- $17.4M capital raise (Nov ‘14) funds CIR through 2017 and completion of Phase 1 and 2A clinical studies
- VGX-100 is a Phase 2 ready oncology asset poised for licensing/partnership
- Eli Lilly partnered compound IMC-3C5 to complete Phase 1 in solid tumours in 1H15
- Strong management team with substantial experience in developing drugs targeting the VEGF pathway, wet AMD and oncology
- Internationally recognised Clinical Advisory Board

OPT-302 Wet AMD Program:
- Initiation Phase 1 clinical trial: 2Q15
- Ph I Primary Data Analysis: 1Q16
- Ph 2A Primary Data Analysis: 2Q17
Financial Position (Unaudited, Feb 2 2015)

- Ticker Symbol: ASX: CIR, OTCQX: CKDXY
- Share Price: A$0.16 (as at Feb 2 2015)
- Total Shares on Issue: 148,086,328
- New Options on Issue: 49,726,669
- Market Capitalisation: A$23m
- Trading Range: A$0.15 – 0.255 (last 12 months)
- Top 10 Shareholders Own: 68%
- Cash: A$20.4m
- Listed Investments: ~A$1.9m
Lead Program: OPT-302 for Wet AMD

- **Lead molecule:**
  - OPT-302 (soluble VEGFR-3, VEGF-C/-D ‘Trap’)

- **Mechanism:**
  - Blocks VEGF-C and VEGF-D:
    - Inhibits blood vessel growth
    - Inhibits vessel leak

- **Strategy:**
  - To develop OPT-302 for use in combination with existing VEGF-A inhibitors for the treatment of wet AMD
  - Achieve complete blockade of the VEGF pathway
The normal retina and ‘Wet’ (neovascular) AMD

Normal Retina

- Photoreceptors
- Retinal Pigment Epithelium
- Bruch’s Membrane
- Choroid

‘Wet’ AMD

- Displaced Photoreceptors
- Retinal Pigment Epithelium
- Bruch’s Membrane
- Choroid
- Fluid accumulation within retinal layers
- Disorganized leaky blood vessels
- Drusen

Figure: The Angiogenesis Foundation
Wet (neovascular) AMD

no AMD  wet AMD

Photo: The Angiogenesis Foundation
Routine Non-Invasive Monitoring Procedures for Disease and Treatment Efficacy

Eye Chart (Visual Acuity)

Retinal Image
Routine Non-Invasive Monitoring Procedures for Disease and Treatment Efficacy

OCT (Optical Coherence Tomography)
(Fluid, hemorrhage, retinal thickness, retinal detachment)
The opportunity for OPT-302: An unmet medical need remains despite anti-VEGF-A therapy

- Wet AMD is the leading cause of blindness in the western world
- Estimated >$US5BN p.a. market opportunity in wet AMD in US alone, increasing with ageing population
- Only two targeted therapies approved for wet AMD (Lucentis® & Eylea®, off-label Avastin®)
- Both target VEGF-A, but not VEGF-C or VEGF-D

**Long term single-agent therapy with VEGF-A inhibitors is associated with sub-optimal response:**

- >50% patients do not achieve a significant gain in vision
- Phase 3 trial results indicate that between 50-70% patients have retinal fluid despite anti-VEGF-A therapy

- VEGF-C & VEGF-D are implicated in mediating resistance to anti-VEGF-A therapy
- VEGF-A, VEGF-C & VEGF-D share signalling through VEGFR-2, a validated pathway involved in wet AMD progression
- VEGF-C & VEGF-D also activate VEGFR-3
- Complete receptor blockade requires blockade of all ligands
The Opportunity for OPT-302

- Potential to develop as a monotherapy
- Combination therapy has the potential to improve clinical outcomes in Wet AMD patients
  - **Visual Acuity**
    - % patients that experience significant vision gain (> 15 letters ETDRS eye chart)
    - Magnitude of vision gain (Mean change visual acuity (letters) from baseline)
  - **Anatomical Outcomes**
    - Central retinal thickness/fluid (OCT)
    - CNV area (Fluorescein Angiography)
  - **Reduce Treatment Burden**
    - Less frequent dosing
  - **Overcome Chronic Vision Loss & Persistent Leakage**

**OBJECTIVE:**

OPT-302 combined with existing agents for wet AMD results in:

Complete blockade of the main pathway driving blood vessel growth
OPT-302 has comparable single-agent and additive activity with Eylea® in mouse AMD

Combined inhibition of VEGF-A (Eylea®), VEGF-C and VEGF-D (OPT-302) is more effective than inhibition of VEGF-A alone

* Pairwise comparison: OPT-302 vs Eylea + OPT-302 (p<0.02)
  Eylea vs Eylea + OPT-302 (p<0.05)
Ophthotech and Opthea: Distinct approaches for wet AMD combination therapy

"Macugen®" – targets VEGF-A_165 isoform
"Fovista®" – aptamer targeting PDGF-b

### OPT-302 Clinical Trials in Wet AMD Patients

- Phase 1 and Phase 2A clinical trials will enrol wet AMD patients
- Dosed via IVT monthly for 3 to 4 doses
- Safety & multiple outcomes to monitor clinical efficacy
  - Visual acuity, central retinal thickness and lesion area
- Phase 1 to test safety and early indicators of efficacy as monotherapy & in combination with Lucentis®
- Phase 2A is randomised and controlled to evaluate safety & efficacy
  - OPT-302 + Lucentis® vs Lucentis® only in previously untreated (naïve) patients
  - OPT-302 as ‘rescue’ therapy in Lucentis ® ‘sub-responders’

#### OPT-302 Wet AMD Program:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Initiation Phase 1 clinical trial:</td>
<td>2Q15</td>
</tr>
<tr>
<td>Ph I Primary Data Analysis:</td>
<td>1Q16</td>
</tr>
<tr>
<td>Ph 2A Primary Data Analysis:</td>
<td>2Q17</td>
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</table>
**OPT-302 Phase 1: Multiple Dose Combination & Monotherapy Study of Safety, PK & Efficacy**

**Primary Outcomes:**
Safety: Ocular & Systemic AEs

**Secondary Outcomes:**
Mean change from baseline in:
- visual acuity
- central retinal thickness
- CNV area

*Pharmacokinetics*

*Anti-Drug antibody formation*

*Biomarkers*

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**OPT-302 (Dose level 1)**
+ Lucentis® (0.5 mg)
*IVT Q4W x3*

**OPT-302 (Dose level 2)**
+ Lucentis® (0.5 mg)
*IVT Q4W x3*

**OPT-302 (Dose level 3)**
+ Lucentis® (0.5 mg)
*IVT Q4W x3*

Primary Analysis after all subjects complete 4 week DLT Window

Long term follow-up to 12 weeks
Phase 2a Efficacy Study: OPT-302 Combination versus anti-VEGF-A Monotherapy (including extension sub-study of OPT-302 ‘Rescue’ therapy for a-VEGF-A “sub-responders”)

Key Endpoints:
Mean change from baseline in:
• visual acuity
• central retinal thickness & fluid
• CNV area

Safety: Ocular & Systemic AEs
Pharmacokinetics
Anti-Drug antibody formation
Biomarkers

* Dose level to be determined from Phase 1
Clinical Advisory Board & Advisors

- Clinical Advisory Board of internationally recognised and experienced key opinion leaders from Australia and US

- Extensive experience in development of novel and FDA approved therapeutics for wet AMD, including Macugen®, Fovista®, Eylea® and Lucentis®

Pravin Dugel MD
Retinal Consultants Arizona
Keck School of Medicine USC

Mark Gillies MD
Save Sight Institute
Sydney Univ.

Peter Campochiaro MD
John Hopkins
Wilmer Eye Institute

Kameran Lashkari MD
Schepens Eye Res.Inst.
Harvard Med.School
Mass Eye & Ear

- Additional advisors in ophthalmology include:

Emmett Cunningham MD
Chairman Ophthalmology Innovation Summit, San Francisco

David Worsley MD
Retinal Ophthalmologist
Hamilton Eye Clinic, NZ

Denis O’Shaughnessy
Founding member Eyetech, SVP Clinical Affairs Oraya

Robert Finger MD
Retinal ophthalmologist
CERA, Vic Eye & Ear Hosp.
<table>
<thead>
<tr>
<th>Company</th>
<th>Treatment</th>
<th>Phase 1/2/3 Estimate</th>
<th>Phase 1/2/3 Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDGF-B aptamer</strong></td>
<td>Wet AMD</td>
<td>$1.4BN</td>
<td>(Phase 3)</td>
</tr>
<tr>
<td><strong>a-VEGF-A gene therapy</strong></td>
<td>Wet AMD</td>
<td>$807M</td>
<td>(Phase 1/2)</td>
</tr>
<tr>
<td><strong>ROCK inhib., small mol.</strong></td>
<td>Glaucoma</td>
<td>$493M</td>
<td>(Phase 3)</td>
</tr>
<tr>
<td><strong>Sustained delivery</strong></td>
<td>Wet AMD</td>
<td>$378M</td>
<td>(Phase 3)</td>
</tr>
<tr>
<td><strong>Gene therapy</strong></td>
<td>Eye diseases</td>
<td>$294M</td>
<td>(Phase 1/2)</td>
</tr>
<tr>
<td><strong>Squalamine</strong></td>
<td>Wet AMD</td>
<td>$219M</td>
<td>(Phase 2)</td>
</tr>
<tr>
<td><strong>OPT-302</strong></td>
<td>Wet AMD</td>
<td>~$23M</td>
<td>(Phase 1 start 2Q’15)</td>
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* At Sept 15 2014, A$, assume A$1 = US$1.08
# OPT-302: Intellectual Property

## Summary covering sVEGFR-3 IP for Eye Disease

<table>
<thead>
<tr>
<th>Composition of Matter</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering sVEGFR-3 (incl. OPT-302)</td>
<td></td>
</tr>
<tr>
<td>• Granted Patents: Europe, Japan, Canada, Australia</td>
<td>2022</td>
</tr>
<tr>
<td>• Case allowed in US Sept 2014 – Grant Expected Jan 2015</td>
<td>~2026</td>
</tr>
<tr>
<td>Covering OPT-302</td>
<td></td>
</tr>
<tr>
<td>• Recently filed new specific composition of matter PCT international patent application</td>
<td>~2034</td>
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### “Use” Patent

US Patent granted covering generic use of sVEGFR-3 capable of binding VEGF-C to inhibit blood vessels in mammal having disease characterised by expression of VEGFR-3 in blood vessels

<table>
<thead>
<tr>
<th>Patent Term Extension/Exclusivity</th>
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<tbody>
<tr>
<td>+5 years under patent term extension</td>
<td></td>
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<tr>
<td>OPT-302 entitled to data exclusivity (DE) and market exclusivity (ME) in many jurisdictions, e.g.:</td>
<td>2023</td>
</tr>
<tr>
<td>• US (12 years DE for biologics)</td>
<td></td>
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<tr>
<td>• Europe (10 years made up of 8 years DE + 2 years ME)</td>
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<tr>
<td>• Japan (up to 8 years de facto DE)</td>
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<tr>
<td>• South Korea (5 years DE)</td>
<td></td>
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<tr>
<td>• Canada (up to 8 years made up of 6 years DE + 2 years ME)</td>
<td></td>
</tr>
<tr>
<td>• Australia (5 years DE)</td>
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Summary

- Leader in VEGF-C/D and VEGFR-3 targeting compounds in ophthalmology and oncology
- Lead compound OPT-302 is a fully owned asset with development potential for a range of eye diseases
- Fully funded through 2017 and Phase 1 and 2A clinical studies in wet AMD patients
  - Initiating Phase 1 clinical trial for wet AMD 2Q15
  - Primary analysis Phase 1 data 1Q’16
  - Primary analysis Phase 2A data 2Q ’17
  - Differentiated MOA & strong IP position
  - World class CAB & advisors
- Two oncology assets in clinical development
  - VGX-100 Phase 2 ready oncology asset poised for licensing/partnership
  - Eli Lilly partnered IMC-3C5 to complete Phase 1 in solid tumours in 1H15
Thank-you

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